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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/546,139	CHATEAU ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14 and 38-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13, 14 38-49* is/are rejected.

7)☒ Claim(s) *42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 24 March 2009.

Claim Status

Claims 13-14 and 38-49 are pending. Claims 13, 42-43 and 49 are amended. Claims 1-12 and 15-37 are cancelled. Claims 13-14 and 38-49 are under current examination.

Priority

This application claims benefit as a 371 of PCT/FR04/00354 (filed 02/17/2004). The instant application has been granted the benefit date, 17 February 2004, from the application PCT/FR04/00354.

RESPONSE TO ARGUMENTS

Claim Objections

The objection to claim 49 is withdrawn because the applicant has submitted claim amendments which changed the claim language to correct the grammatical error.

Double Patenting

The rejection of claims 13-14 and 38-49 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1, 12-14 and 38-49 of copending Application No. 10/781499 (US2005/0054060) is withdrawn in response to the applicants arguments and/or claim amendments.

The applicant filed a terminal disclaimer on 4/9/2009.

Therefore, the examiner hereby withdraws the rejection of claims 13-14 and 38-49 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1, 12-14 and 38-49 of copending Application No. 10/781499 (US2005/0054060).

35 USC § 112, 1st paragraph

The rejection of claim 42 under 35 USC 112, 1st paragraph (new matter) is withdrawn in response to the applicants claim amendments.

The applicant's claim amendments have been fully considered and are persuasive. The applicant has amended the claims so that the co-substrate is added in step (b). The specification supports this claim language.

Therefore, the examiner hereby withdraws the rejection of claim 42 under 35 USC 112, 1st paragraph (new matter).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-14, 38-41 and 43-49 remain rejected under 35 U.S.C. 103(a) as being obvious over unpatentable over Richaud et al. (J. Biological Chemistry. December 25,

1993; 268(36):26827-26835) in view of Short et al. (US2005/0124010, published June 19, 2005) for the reasons of record and the comments below. In addition, because Claim 42 has been amended and is now a duplicate of claim 41, the pending rejection has been extended to reject this claim.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant states "Richaud does not attempt to 'evolve' any metabolic pathways. On the contrary to purpose of Richaud is 'to install a biosynthetic pathway for the thioether analog of meso-diaminopimelate, meso-lanthionine (Fig.1), in the metabolism of *E. coli*' Richaud at 26828" (Remarks, page 7). The basis of the applicant's argument seems to be that Richaud does not use the word, "evolve" in their reference. Given the breadth of the claims and the lack of specifics in the applicant's arguments regarding the deficiencies of Richaud, the examiner finds this argument unpersuasive.

Further, the applicant argues, "that while Richaud does not teach step (d) of independent claim 13, Richaud, in fact does not teach steps (a) through (c) as required by claim 13 either" (Remarks, page 7 bridging page 8). The examiner has provided detailed citations for each of the limitations of claim 13(a)-(c) in Richaud and claim 13(d) in Short in the pending rejection, reiterated below. The examiner respectfully requests that the applicant point out specific deficiencies of these references. Accordingly, the examiner finds the applicant's argument unpersuasive.

The argument states, "if no alteration of enzyme specificities occurred, if no natural selection occurred, than (*sic*) neither could the evolution of a metabolic pathway

occur. Therefore, no evolved microorganism was produced as required by the claim" (Remarks, page 8, parag.1, emphasis provided by applicant). The applicant then provides a table at the bottom of page 8, which contrasts the present invention with the teachings of Richaud. The examiner points out that there are method steps recited in this table which are not recited in the pending claims. For example, as indicated in the table, step (b) requires cultivation of the genetically modified microorganism for numerous cycles in a flask. This is not reflected in the claims. Perhaps this is part of the natural selection process to which the applicant refers. As written, the claims are broad and the cited art satisfies the literal claim limitations. Based on the applicant's remarks, it seems the claims do not fully capture the natural selection process to which to applicant has applied the concept of "evolution of a metabolic pathway." The applicant seems make an intellectual leap from the literal meaning of the claims to a metaphorical meaning which the applicant sees in his claims. It is vital that the applicant find language which makes the critical feature of the invention concrete in the claim language. The applicant is relying on the word, "evolve" to describe something critical to his invention, but this is not a concrete method step. The examiner can perceive frustration in the applicant's response because the applicant has some intended meaning which is being ignored by the examiner. To obtain a valid patent the applicant will need to successfully claim this concept in concrete language. Therefore, the examiner finds the applicant's arguments unpersuasive, because the applicant seems to be arguing limitations which are not recited in the claims. In response to applicant's argument that the references fail to show certain features of applicant's

invention, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The applicant further argues that Short does not teach isolation of the evolved polypeptide. In particular, the applicant does not view the various methods, such as gel electrophoresis as a form of isolation. Contrary to the applicant's view, the examiner interprets gel electrophoresis of the expressed polypeptide is as a form of isolation. Therefore, the examiner finds the applicant's argument unpersuasive.

Throughout the applicant's remarks, the applicant has argued that Richaud teaches a method of genetically engineering a microorganism, while the instant invention is directed to evolution of a microorganism. The examiner has given a broad, but reasonable interpretation to the pending claims. As a result, the examiner found that the clam language can encompass some forms of genetic engineering. This is clearly the issue of contention that needs to be overcome. The examiner hopes the applicant can focus future claim amendments on language which will sufficiently distinguish the applicant's invention from genetic engineering microorganisms.

Therefore, the examiner hereby maintains the rejection of claims 13-14, 38-41 and 43-49 under 35 U.S.C. 103(a) as being unpatentable over Richaud et al. in view of Short et al. Claim 42 has been amended and is now a duplicate of claim 41; therefore, the pending rejection has been extended to reject this claim.

The examiner reiterates the pending rejection:

Claims 13-14, and 38-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richaud et al. (J. Biological Chemistry. December 25, 1993; 268(36):26827-26835) in view of Short et al. (US2005/0124010, published June 19, 2005).

Claim 13 is directed to a method for the producing an evolved protein comprising a) generating a directed genetic modification in a gene of interest in an initial microorganism to yield a modified microorganism, wherein the production or consumption of a substrate is inhibited when the modified microorganism is grown on a defined medium, wherein the ability of the modified microorganism to grow is impaired; b) culturing the modified microorganism obtained in step (a) on the defined medium allowing the modified microorganism to evolve a metabolic pathway, wherein the defined medium can contain a co-substrate promoting the evolution; c) selecting an evolved microorganism from step (b) able to grow on the defined medium, wherein at least one protein has evolved in the metabolic pathway compensating for the inhibition allowing the modified microorganism to proliferate; d) isolating the evolved protein.

The specification defines an evolved protein as “a sequence of amino acids (protein sequence) that differs in at least one amino acid from the initial protein sequence after selection” (page 4, lines 5-8). According to the specification, selection is defined as “a culture method used to select microorganisms that have evolved in such a way that a modification does not affect growth anymore” (page 3, lines 22-24). The specification does not explicitly define the phrase “directed genetic modification.” Accordingly, the examiner will interpret these terms broadly.

Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13. Richaud et al. teach "a latent metabolite could under certain circumstances fulfill an essential need in cell chemistry, the way would be open for establishing a biosynthetic pathway *de novo*" (page 26827, col.1), which satisfies the limitations of part b) claim 13, directed to evolution of a metabolic pathway. Richaud et al. also teach "expansion of thioether biosynthesis in *Escherichia coli* generates sulfur-containing amino acids that can replace meso-diaminopimelate, the essential amino acid used for cross-linking the cell wall," and "[a]s a result, meso-lanthionine and L-allo-cystathione were produced endogenously and incorporated in the peptidoglycan, thereby enabling *E.coli* strains auxotrophic for diaminopimelate to grow in its absence" (abstract), which the examiner interprets as satisfying the limitations of part c) of claim 13 directed to "wherein at least one protein has evolved in the metabolic pathway allowing the modified microorganism to proliferate." Richaud et al. describe this process, "techniques of metabolic engineering can be applied to evolving the chemical constitution of living cells beyond its present state" (abstract), which is similar to the broad outline of the instant invention provided by the specification. Furthermore, Richaud et al. teach "a metC mutation enhances the growth of *dap* strains exogenously supplied with L-lanthionine, meso-lanthionine, or L-allo-cystathionine as the cross-linking amino acid' and is absolutely required for growing such strains with exogenous L-cystathionine (Table VI). The broad activity of cystathionase, which is indeed known

to degrade generically L-cysteine thioethers in vitro, can thus be rationalized as fulfilling a corrective task, which adds to the biosynthetic function of the enzyme in E. coli metabolism " (page 26834, col.1, parag.1), which the examiner interprets as satisfying the limitations of part a) and b) of claim 13, directed to "wherein the production or consumption of a substrate is inhibited when the modified microorganism is grown on a defined medium, wherein the ability of the modified microorganisms to grow is impaired" and "wherein the defined medium can contain a co-substrate." Richaud et al. further indicate, [t]hese strains can thus be viewed as having undergone an evolutionary commitment to use cysteine thioethers for building their cell wall. Although this commitment did not result from natural selection but was rationally set up in their genome, the fitness of the committed strains might now be improved by natural selection" (page 26834, col.2, parag.1).

The only element of claim 13 not taught by Richaud et al. is part d), directed to isolation of the evolved protein.

Claims 38-39 are directed to the method of claim 13, wherein the gene of interest (claim 38) or evolved protein (claim 39) is homologous or heterologous. The specification teaches "[t]his invention also concerns a method comprising an additional step a1) in which at least one heterologous gene coding for a heterologous protein is introduced, which heterologous gene is intended to cause the evolution of a new metabolic pathway" (page 2, lines 9-11). Richaud et al. teach "jointly overexpressing the *metB* gene coding for L-cystathionine γ-synthase and disrupting the *metC* gene"

(abstract). In this case, the disrupted *metC* gene is the homologous gene of interest and the overexpressed *metB* gene the heterologous evolved protein.

Claim 40 is directed to the method of claim 13, wherein the defined medium is substantially free of the substrate the production or consumption of which is inhibited in the modified microorganism. In the example of Richaud et al., the substrate is meso-diaminopimelate. Richaud et al. teach “thereby enabling *E.coli* strains auxotrophic for diaminopimelate to grow in its absence” (abstract). It seems that the substrate is not present in the medium of these *E.coli* strains.

Claims 41 and 42 are duplicate claims. Both are directed to the method of claim 13, wherein in step (b) a co-substrate is added to the defined medium. Richaud et al. teach "[g]rowth of *E. coli* mutants bearing a deletion of the diaminopimelate pathway in the presence of lysine and in the absence of diaminopimelate there provide an inescapable selection screen for the endogenous production of diaminopimelate substitutes." (bottom page 26827 bridging 26828). This seems to satisfy the limitations of claim 41.

Claim 43 is directed to the method of claim 13, wherein the protein having evolved in the compensatory pathway is encoded by a gene being homologous gene or heterologous gene. The specification teaches “[t]his invention also concerns a method comprising an additional step a1) in which at least one heterologous gene coding for a heterologous protein is introduced, which heterologous gene is intended to cause the evolution of a new metabolic pathway” (page 2, lines 9-11). Richaud et al. teach “jointly overexpressing the *metB* gene coding for L-cystathionine γ-synthase and disrupting the

metC gene" (abstract). In this case, the overexpressed *metB* gene encodes the heterologous evolved protein.

Claim 44 is directed to the method of claim 13, wherein the genetic modification comprises the directed mutation or deletion of a gene of interest or the directed modification of a promoter in the gene of interest. Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13.

Claim 45 is directed to the method of claim 13, wherein the genetic modification consists in the removal of most of the gene of interest. Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13. The type of mutation does not seem to be particularly important to the practice of the method. Any type of null mutant, whether created by a deletion, point mutation, etc would be obvious in light of the teachings of Richaud et al.

Claim 46 is directed to the method of claim 13, wherein the gene of interest is replaced with a selection marker gene. The type of mutation does not seem to be particularly important to the practice of the method. Any type of null mutant, whether created by a knockout by replacing the gene of interest with a selection marker, or by any other known means, would be obvious in light of the teachings of Richaud et al.

Claim 47 is directed to the method of claim 13, wherein the microorganism is selected among bacteria, yeasts, and fungi. Richaud et al. teach a method which uses *E. coli.*

Claim 48 is directed to the method of claim 13, wherein the microorganism is…[various microorganisms] including *Escherichia sp*. Richaud et al. teach a method which uses *Escherichia coli.*

Claim 49 is directed to the method of claim 13, wherein the microorganism is *E. coli* and *C. glutamicum.* The instant specification does not describe a method that uses two different microorganisms, so the examiner is interpreting the instant claim as reciting "or" rather than "and." In particular, the specification describes using either *E. coli* or *C. glutamicum* on page 8, lines 8-10 of the specification. Richaud et al. teach a method which uses *E. coli.*

Richaud et al. does not teach all the limitations of claim 13. The only element of claim 13 not taught by Richaud et al. is part d), directed to isolation of the evolved protein.

However, Short et al. teach "directed evolution…generating transgenic organism, such as microbe" (abstract). Short et al. further teach isolating cells which produce a desired metabolite (paragraphs 1062-1063) and also teach measuring metabolic parameters such as growth, as well as "changes in the expression of the polypeptide can be measured by any method, e.g., a one-dimensional gel electrophoresis,…western blot" (parag.1070). Short et al. teach that cystathionine synthase is an example of the

gene or gene product used in their methods. Gel electrophoresis of the expressed polypeptide is a form of isolation.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Richaud et al and Short et al. so that the evolved protein produced by the microorganisms of Richaud et al are isolated.

The person of ordinary skill in the art would have been motivated to make those modifications because Short et al. suggest measuring expression levels of the evolved protein, as an alternative or in addition to measurement such as growth on defined media.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Richaud et al. and Short et al. because each of these teachings generated evolved microorganisms and discuss the proteins which make possible the growth of the auxotrophic organisms.

Therefore the method as taught by Richaud et al. in view of Short et al. would have been *prima facie* obvious over the method of the instant application.

NEW GROUNDS OF REJECTION

Claim Objections

Claim 42 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 41. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Examiner, Art Unit 1633
/Janet L. Epps-Smith/
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